## REMARKS/ARGUMENTS

By this Amendment, the specification and claims 2-4, 7-8, 24-26, 28, 32, 34-35, 36 and 37 are canceled, and claims 1, 5-6, 9, 23, 27, 29-31, 33, 38 and 43 are amended. Claims 1, 5-6, 9-23, 27, 29-31, 33, 36 and 38-43 are pending.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

**Priority**

A proper cross-reference to the related provisional application is included in the foregoing specification amendment. Accordingly, reconsideration and withdrawal of the objection to the priority claim are respectfully requested.

**Claim Rejections – 35 U.S.C. § 101**

The rejection of claim 32 under 35 U.S.C. § 101 is rendered moot by the cancellation of claim 32. Accordingly, reconsideration and withdrawal of the utility rejection are respectfully requested.

**Claim Rejections – 35 U.S.C. § 112**

Claims 1-6, 10, 14-22, 28-32, 35, 36 and 43 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The rejection is rendered moot by the foregoing claim cancellations and amendments. None of the pending claims refers to "a low dose" of ribavirin.

Accordingly, reconsideration and withdrawal of the indefiniteness rejection are respectfully requested.

**Claim Rejections – 35 U.S.C. § 102**

Claims 1-4, 10, 14-25, 28, 32-35 and 39-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Ganguly et al. (WO 00/23455). The rejection is rendered moot by the incorporation of the limitations of claim 7 into independent claims 1, 23, 33 and 43. The dosage limitations of these claims are not disclosed by Ganguly et al.

Accordingly, reconsideration and withdrawal of the anticipation rejection of claims 1-4, 10, 14-25, 28, 32-35 and 39-43 over Ganguly et al. are respectfully requested.

Claims 1, 2, 10, 14-17, 18, 20, 32 and 43 stand rejected under 35 U.S.C. § 102(b) as being anticipated by McHutchison et al. (New Eng J Med 339:1435-92). This rejection is respectfully traversed.

McHutchison et al. reports a trial involving chronic hepatitis C patients who received alpha-2b interferon alone or in combination with ribavirin. The ribavirin dose administered was 1000 to 1200 mg orally per day and for severe adverse events, the dose was reduced to 600 mg per day. Accordingly, the McHutchison et al. paper teaches that useful daily doses of ribavirin are 1000 or 1200 mg per day. Moveover, there is nothing in McHutchison to suggest the form of the composition. For example, McHutchison does not disclose a slow-release formulation of ribavirin.

Accordingly, reconsideration and withdrawal of the anticipation rejection of claims 1, 2, 10, 14-17, 18, 20, 32 and 43 over McHutchison et al. are respectfully requested.

**Claim Rejections – 35 U.S.C. § 103**

Claims 1-4, 7-28, 32-35 and 37-43 stand rejected under 35 U.S.C. § 102(b) as being anticipated, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Ganguly et al. This rejection is respectfully traversed.

Ganguly et al. fails to teach or suggest the use of less than 400 mg of ribavirin per day in a slow-release formulation. The present invention is based at least in part on the inventor's proposal that the use of ribavirin in a slow-release form containing less than 400 mg per day, together with interferon, allows a selective anti-viral effect to be obtained in the liver. Prior to the present invention, it was seen as necessary to achieve systemic levels of ribavirin in order to attain an anti-viral effect in the liver. To this end, the level was previously seen as being an impediment to achieving suitable systemic levels. The present invention involves delivering ribavirin as a low dose in slow-release formulation. The relatively small volume of the portal vein can be used to advantage in providing a sufficient dosage and achieving an anti-viral effect in the liver without the need to achieve clinically effective blood levels in the peripheral circulation. Ganguly et al. does not recognize the ability to obtain a liver selective effect. Indeed, on page 1, Ganguly et al. explains that side effects of ribavirin cause significant problems of hemolysis and anaemia and that the answer is to provide a more potent ribavirin derivative. Ganguly et al. does not recognize the liver selective effect that can be obtained by

administering less than 400 mg in a slow-release format and indeed prefers higher dosages than 400 mg.

Moreover, Ganguly et al. is not really instructive regarding the use of slow-release formulations of ribavirin. The only mention of a formulation which may be relevant is the following statement on page 35:

> [O]ther types of administration of both medicaments as they become available are contemplated such as transdermally, by suppository, by sustained release dosage form and by pulmonary inhalation.

A mere reference to sustained release dosage form of both of the medicaments suggests the use of the combination therapy in a sustained release. Furthermore, it is not clear what format the sustained release is intended to take, whether it is intravenous, oral, transdermal or by some other route of administration. Ganguly et al. does not recognize that the effects relating to systemic administration of ribavirin may be avoided by using a slow-release composition of ribavirin in an oral dose of less than 400 mg so as to provide a sufficient level in the portal vein without leading to clinically effective levels in the peripheral circulation. Furthermore, this advantage is not inherent in the compositions of Ganguly et al., as the reference does not teach the use of slow-release formulations of ribavirin.

Accordingly, reconsideration and withdrawal of the anticipation/obviousness rejection of claims 1-4, 7-28, 32-35 and 37-43 over Ganguly et al. are respectfully requested.

Claims 5, 6 and 36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Ganguly et al. in view of Wong et al. (US 6120803). This rejection is respectfully traversed.

Wong describes a delivery device that remains in the stomach for an extended period of time. Wong does not teach or suggest the dose of ribavirin that may be used, and if it were considered to use ribavirin under conventional technology, it would be considered necessary to use a dose sufficient to achieve a level of the drug in the peripheral circulation. For example, doses of 1000-1200 mg per day as proposed by McHutchison. Indeed as prolonged release of an active leads to lower levels of the active being present at any one time, it would be expected that higher levels of the drug would be required in order to obtain therapeutically effective levels. It is only once the principle of liver selective therapy is recognized in accordance with the present

invention that a combination of slow-release and low dose can be used to provide effective treatment of liver disease.

Accordingly, reconsideration and withdrawal of the obviousness rejection of claims 5, 6 and 36 over Ganguly et al. in view of Wong et al. are respectfully requested.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.